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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,599	05/31/2005	Joseph M. Penninger	SONN:064US	8087

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,599	PENNINGER ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67-69 and 73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-69 , 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of the invention of group II (claim 67-69) filed on February 3, 2006 is acknowledged. The traversal is on the grounds(s) that Examiner has not set forth convincing argument that the search and examination of group II and other groups such as IV necessarily represents an undue burden for the examiner and that examination of other groups along with elected group directed to a method of treating an ACE2 decreased state by administering ACE2 activator and ACE inhibitor would not require separate searches for prior art. Applicant argument of examining group II with group IV is found persuasive and therefore these groups are rejoined for examination purposes. The restriction requirement between group I and II is withdrawn in view of applicants clarification and deletion of term agonist from the pending claim 67.

Accordingly, a method of treating an ACE2 decreased state comprising administering to a mammal therapeutically effective amount of ACE2 activator and by co-administering ACE2 activator with ACE inhibitor will be examined in the instant application.

2. Claims 1-66, 70-72 and 74-97 have been cancelled by the amendment filed on February 3, 2006.

3. Claims 67-69 and 73 drawn to a method of treating an ACE2 decreased state comprising administering to a mammal therapeutically effective amount of ACE2 activator and co-administering ACE2 activator with ACE inhibitor are pending.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 67-69 and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claimed inventions encompass a method of treatment of an ACE2 decreased state by administering to a mammal therapeutically effective amount of any ACE2 activator. In the instant case, the claim is broadly directed to a method of treating plurality of conditions by administering mammals any ACE2 activator. This genus comprises plurality of activators that may further have subspecies. The claims and specification broadly discloses ACE2 activators that encompass ACE2 nucleic acid, its fragments, ACE 2 polypeptides, its fragment, and compounds that enhances ACE2 activity. The specification merely contemplates that activators would preferably be directed to specific domains of ACE2 and target unique sequences of ACE2 (pp 15 of the specification, lines 10-14) to increase ACE2 activity. The specification does not describe the complete structure of any ACE2 activator except mouse and rat ACE2

nucleotide sequence. A skilled artisan could not predict the structure of the any other ACE2 activator nor could a skilled artisan predict the structure of any domain or unique sequence in all different species. The specification does not provide any disclosure as to what would have been the required structure for an activator and whether the structure is present in various species of mammals or how does it vary. Therefore, possession of an ACE2 nucleic acid, peptide does not predict the structure and characteristics of administering any other variant to mammal showing contemplated biological activity. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow person of ordinary skill in the art to recognize that he or she invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (other than nucleotide sequence), specific feature and functional attributes that would distinguish different members of claimed genus. In the instant case, the only other identifying characteristics is that the ACE2 gene sequence is a negative regulator that antagonizes the RAS and heart failure which cannot be an identifying characteristics since many other genes will have that characteristics. No identifying characteristics of a compound or other fragments or variant of ACE2 are disclosed. Further without a clear teaching of the

essential elements of the claimed ACE2 activator and lack of identifying characteristics, a skilled artisan cannot envision the detailed structure of all the variants, fragments and compounds that must show the contemplated biological activity. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity/simplicity of the structure and/or methods disclosed in specification.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of all the different ACE2 activator effective in mammals, at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 67-68 are rejected under 35 U.S.C. 102(b) as being anticipated by Acton et al (US Patent no. 6194556, dated 02/27/2001, effective filing date 12/11/ 1997).

Claim 67 is directed to a method of treating an ACE2 decreased state comprising administering to a mammal having an ACE2 decreased state a therapeutically effective amount of ACE2 activator. Claim 68 limits the mammal of claim 67 to include human.

Acton et al teach a method for treating disease or disorder that is associated with aberrant ACE-2 level or activity or which can benefit from modulation of the activity or level of ACE-2 (col. 7 lines 41-43). Acton et al describe the term "modulation" to refer both up regulation (activation) and down regulation (col. 14, lines 28-32). Thus, teaching of Acton et al encompass a method of treating an ACE2 decreased state comprising administering a therapeutic effective amount of ACE2 agonist. Acton et al further teach the methods for treating hypertension, CHF, inflammatory reactions, and methods to reduce pain. The methods of Acton et al comprise administering pharmaceutically effective amount of a composition comprising an ACE-2 therapeutic either locally or systemically to a subject (col. 7, lines 45-52). Thus, teachings of Acton et al encompass all the limitation of the instant application.

Accordingly, Acton et al anticipate claims 67-68.

8. Claims 67-68 and 73 are rejected under 35 U.S.C. 102(e) as being anticipated by Acton et al (US Patent application no. 6,632,830, dated 10/14/2003, filing date 04/28/2000).

Claim 67 is directed to a method of treating an ACE2 decreased state comprising administering to a mammal having an ACE2 decreased state a therapeutically effective amount of ACE2 activator. Claim 68 limits the mammal of claim 67 to include human.

Claim 73 further limits the claim 67 to include co administration of ACE2 activator and an ACE inhibitor.

Acton et al describe "ACE-2 modulating compound" to compounds, which modulate, e.g., inhibit, promote, or otherwise alter the activity of ACE-2. ACE-2 modulating compounds include both ACE-2 agonists and antagonists (col.5, lines 53-55). Acton et al describe, "ACE-2 associated state" to include conditions that are associated with ACE-2 and disorders which are characterized by aberrant levels of ACE-2 activity. Acton et al define ACE-2 associated states to include high blood pressure, high blood pressure related diseases and disorders, and, in particular, arterial hypertension and congestive heart failure (CHF) (col. 33, lines 65-68 bridging col. 34, lines 1-6). It is noted that the method of Acton contemplates method of treating CHF by administering ACE inhibitory compounds concurrently with ACE-2 modulating compound (col. 35, lines 30-32). In addition, Acton et al teach that ACE-2 is expressed in kidney and is homologous to ACE. It is noted that Acton et al teach ACE-2 modulating compounds could be used for treating and preventing renal diseases or disorders, either alone or in combination with known ACE inhibitors. Thus teaching of Acton et al include administering a ACE2 modulating compound that may be agonist or antagonist of ACE activity in combination with known ACE2 inhibitor for ACE associated disorder.

Accordingly, Acton et al anticipate claims 67-68 and 73.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 67-69 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Acton et al (US Patent application no. 6,632,830, dated 10/14/2003, filing date 04/28/ 2000) and in view of Crackower et al (American Journal of Hypertension, April, 2001, 14 (4) Part 2, pp. 78A).

Claim 67 is directed to a method of treating an ACE2 decreased state comprising administering to a mammal having an ACE2 decreased state a therapeutically effective amount of ACE2 activator. Claim 68 limits the mammal of claim 67 to include human. Subsequent claim 69 limits the decreased ACE2 state to include hypertension, congestive heart failure, chronic heart failure, acute heart failure, myocardial infarction, arteriosclerosis, renal failure, and/or lung disease

Acton et al describe "ACE-2 modulating compound" to compounds, which modulate, e.g., inhibit, promote, or otherwise alter the activity of ACE-2. ACE-2 modulating compounds include both ACE-2 agonists and antagonists (col.5, lines 53-55). Acton et al describe, "ACE-2 associated state" to include conditions that are associated with ACE-2 and disorders which are characterized by aberrant levels of ACE-2 activity. Acton et al define ACE-2 associated states to include high blood pressure, high blood pressure related diseases and disorders, and, in particular, arterial hypertension and congestive heart failure (CHF) (col. 33, lines 65-68 bridging col. 34, lines 1-6). It is noted that the method of Acton contemplates method of treating CHF by administering ACE inhibitory compounds concurrently with ACE-2 modulating compound (col. 35, lines 30-32). It is noted that Acton et al teach ACE-2 modulating compounds could be used for treating and preventing renal diseases or disorders, either alone or in combination with known ACE inhibitors. However, Acton et al do not specifically teach administering ACE2 activator/agonist for the treatment of ACE2 decreased state associated hypertension either alone or in combination with ACE inhibitor. In fact, Acton et al teach contrary to the teaching of instantly recited claim.

Crackower et al disclose cloned rat ACE2 and radiation hybrid mapping placed ACE2 on the X-chromosome with in defined QTL in Sabra salt-sensitive model of hypertension. Crackower et al also describe identification of QTL overlapping in other rat model of hypertension. It is emphasized that ACE2 expression was found to reduce both at transcriptional and translational level in hypertensive group as compared to normotensive group. Crackower et al conclude that reduced ACE2 activity increases

hypertension. It is also noted that Crackower et al describe ACE2 as a novel candidate gene for the treatment of hypertension (abstract).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of treating ACE2 associated disorder by including ACE2 activator/agonist for the treatment of ACE2 decrease associated hypertension as taught by Crackower. Acton et al had already showed the method for treating disorders that are associated with aberrant ACE-2 activity (col. 34, lines 1-3). In addition, Acton et al also disclose a number of ACE2 activator that could be used to enhance ACE2 activity. Crackower et al had described that ACE2 expression is reduced in hypertensive population (abstract). The skilled artisan would have been motivated to modify the method of treating ACE2 decreased state by administering ACE2 activator/agonist by using the method of Acton for the treatment of hypertension as suggested by Crackower. The skilled artisan would have been further motivated to reduce hypertension by co administering ACE inhibitor along with ACE modulating agent as suggested by Acton.

One who would have practiced the invention would have had reasonable expectation of successfully treating ACE2 decreased state by modifying the method of Acton to increase the ACE2 activity by administering ACE2 activator/agonist as Crackower taught that reduced ACE2 activity is associated with hypertension and ACE2 being a novel candidate gene for hypertension (abstract, last line). One of ordinary skill in art would have been motivated to combine the teaching Acton and Crackower because a method of treating ACE2 decreased state associate disorder by ACE2

activator/agonist would have provided ACE2 activity in the heart. This would have allowed skilled artisan to enhance ACE2 activity in the subject thereby reducing the hypertension associated with reduced ACE2 as taught by Crackower.

Therefore, the claimed invention would have been prima fascia obvious to one of ordinary skill in the art at the time of the invention.

11. No Claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 8:30AM-5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Anoop Singh, Ph.D.
Examiner, AU 1632

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER